

REMARKS

Amendments

Claims 1 and 22 are amended herein, without prejudice or disclaimer, to focus on the elected species of a foreign antigen which is a graft. Non-elected claims are cancelled without prejudice or disclaimer. Due to the cancellation of claim 19, a request to delete inventor T. Stewart is filed herewith. The trademarks are removed from claims 7 and 10 responsive to the Examiner's suggestion on page 10 of the Office Action. To advance prosecution, claims 1, 22 and 28 refer to an "antibody" antagonist, in relation to the Section 112, rejections. To obviate the objection to claims 13-15, the space is included as suggested by the Examiner in the first paragraph on page 3 of the Office Action. To obviate the only prior art rejection in the case and hence accelerate allowance, claim 30 is canceled herein without prejudice or disclaimer. In that the amendments do not introduce new matter, their entry is respectfully requested.

Information Disclosure Statement

As requested on page 2 of the Office Action, a clean PTO-1449 form and the missing references have been hand delivered to the Examiner under separate cover. Consideration of all the cited art is respectfully requested.

Section 112, written description

Claims 1-2, 4-16, 20, 22-23, 28 and 30 are rejected under 35 USC Section 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner urges that apart from the disclosure of rituximab (RITUXAN) the instant disclosure fails to provide a representative number of species of antagonist that is capable of binding to CD20 to destroy and/or

deplete B cells in a mammal to reduce effectively a humoral response against any foreign antigen or for treating any graft-versus-host or host-versus-graft disease. The Examiner contends that it is unclear which essential core structural elements that are shared among the CD20 antagonists encompassed by the broad scope of the instant claimed invention yield the desired therapeutic results contemplated by Applicants, other than the common functional limitation of binding to CD20.

Applicants submit that the present claims do find written description in the specification as filed. To expedite prosecution, claims 1 and 28 herein refer to an "antibody" that is used in the method. The structural elements of such molecules are described on at least page 10, line 20 through to line 22 on page 14 as well as pages 21-30. The Office acknowledges that the specification teaches at least the rituximab species. Applicants submit that the specification describes further species to support the claim to the genus of antibodies that bind CD20. For instance, the specification describes the following antibodies that bind CD20: Y2B8, B1, 1F5, chimeric 2H7, L27, G28-2, 93-1B3, B-C1 and NU-B2. See page 15, lines 8-17. Moreover, the antigen - CD20 - is well characterized in the specification (page 4, lines 8-13) and, according to the PTO's Written Description Guidelines (Example 16: Antibodies) generating antibodies to a well characterized antigen such as the CD20 antigen of the present application would be routine. The specification provides ample guidance as to the production of antibodies (page 10, line 20 through to line 22 on page 14 as well as pages 21-30, for instance). Hence, Applicants submit that the specification does provide a representative number of species of antibodies encompassed by the present claims.

The specification explains that antibodies that bind CD20 can be used as antagonists to destroy or deplete B cells and/or interfere with one or more B cell functions, e.g. by reducing or preventing a humoral response

elicited by the B cell (page 8, lines 24-26). The specification also describes how such antibodies can be used to block an immune response to a graft in a mammal (where the mammal is not suffering from a malignancy), comprising administering to the mammal a therapeutically effective amount of the antibody; or how to treat graft-versus-host or host-versus-graft disease in a mammal comprising administering to the mammal a therapeutically effective amount of the antibody (see, e.g., page 4, line 27 through to line 3 on page 5; page 6, line 15, through to line 15 on page 7; pages 40-44; and Example 3).

Hence, Applicants submit that the specification does provide a written description that satisfies Section 112, first paragraph requirements.

Section 112, enablement

Claims 1-2, 4-16, 20, 22-23, 28 and 30 are rejected under 35 USC Section 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner relies on Leget *et al.* (1998) and Friend *et al.* (1999) as allegedly evidencing that "the use of rituximab or any CD20 antagonist in other *in vivo* applications (e.g., graft transplantation) is still very limited and further investigation is required."

The Examiner cites to the statement in Friend *et al.* that in clinical transplantation the impact of monoclonal antibodies on therapeutic regimens has been rather disappointing, and urges that in light of the state of the art at the effective filing date of the present application, there is no evidence of record indicating or suggesting that the use of rituximab or any CD20 antagonist would be effective in reducing or preventing the host humoral and/or T cell-mediated immune responses against a graft (both allogenic and xenogenic) to an extent that a graft would survive and be maintained for a sufficient period of time to yield

any beneficial use or any graft versus host reactions. The abstract of Leget *et al.* is relied on as teaching that even in the B-cell lymphoma treatment studies with Rituximab, despite the depletion of normal B cells, treated patients are still capable of eliciting an immune response against the humanized rituximab, even though this is at a low level, and that Rituximab has no effect on the total mean serum IgG and IgA levels in patients treated with the humanized monoclonal antibody.

Applicants submit that the presently claimed invention is enabled. The present application describes how to block an immune response to a graft in a mammal, wherein the mammal is not suffering from a malignancy, comprising administering to the mammal a therapeutically effective amount of an antibody which binds to CD20; or how to treat graft-versus-host or host-versus-graft disease in a mammal comprising administering to the mammal a therapeutically effective amount of the antibody (see, e.g., page 4, line 27 through to line 3 on page 5; page 6, line 15, through to line 15 on page 7; pages 40-44; and Example 3).

The Examiner relies on Friend *et al.* and Leget *et al.* as purportedly demonstrating that the invention is not enabled. Applicants submit that the cited references fail to provide objective evidence that the presently claimed invention is not enabled. First, in relation to Friend *et al.*, since this is concerned with an anti-CD3 antibody as opposed to the presently claimed antibody that binds to CD20, Applicants submit that it does not show lack of enablement of the presently claimed methods. Turning now to Leget *et al.*, Applicants submit that this reference is not relevant to the present invention, since the claims herein specifically exclude the mammal which is suffering from a malignancy.

In view of the above, Applicants respectfully request that the Section 112, 1st paragraph rejection be reconsidered and withdrawn.

Section 112, 2nd paragraph

The rejection of claims 7 and 10 is moot in view of the removal of the trademarks from the claim as suggested by the Examiner.

As to the Examiner's rejection of claim 13, Applicants submit that the skilled clinician would readily understand what was intended by the expression "a dose substantially less than 375mg/m²" in terms of a therapeutic dose. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 28 is rejected as being incomplete for failing to include the step of transplantation of a graft. Applicants submit that the claim is clear and complete. The claim pertains to treatment of graft-versus-host or host-versus-graft disease in a mammal, and hence, the mammal has the disease or the method prevents the disease. Thus, Applicants submit that it is not necessary to include the step of transplanting the graft.

As to claim 30, the rejection is moot in view of the nonprejudicial cancellation of this claim.

Reconsideration and withdrawal of the rejections is respectfully requested in view of the above.

Section 103

The Section 103 is moot in view of the nonprejudicial cancellation of claim 30.

Applicants believe that this application is now in condition for allowance, and look forward to early notification to that effect.

Respectfully submitted,

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PATENT TRADEMARK OFFICE

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The pending claims have been amended as follows:

1. (Amended) A method of blocking an immune response to a [foreign antigen] graft in a mammal, wherein the mammal is not suffering from a malignancy, comprising administering to the mammal a therapeutically effective amount of an [antagonist] antibody which binds to CD20.

7. (Amended) The method of claim 2 wherein the antibody comprises rituximab [(RITUXAN®)].

10. (Amended) The method of claim 9 wherein the antibody comprises Y2B8 or ¹³¹I-B1 [(BEXXAR™)].

13 (Amended) The method of claim 2 comprising administering a dose of substantially less than [375mg/m²] 375 mg/m² of the antibody to the mammal.

14. (Amended) The method of claim 13 wherein the dose is in the range from about [20mg/m² to about 250mg/m²] 20 mg/m² to about 250 mg/m².

15. (Amended) The method of claim 14 wherein the dose is in the range from about [50mg/m² to about 200mg/m²] 50 mg/m² to about 200 mg/m².

22. (Amended) The method of claim 1 comprising administering the [antagonist] antibody to the mammal before the mammal is exposed to the [foreign antigen] graft.

28. (Amended) A method of treating graft-versus-host or host-versus-graft disease in a mammal comprising administering to the mammal a therapeutically effective amount of an [antagonist] antibody which binds to CD20.

Claims 2-4, 17-21, 23-27, and 30 have been cancelled without prejudice or disclaimer.